PREGNANCY PLUS

Chronic kidney disease in pregnancy

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Pregnant women with chronic renal disease adapt poorly to a gestational increase in renal blood flow. This may accelerate their decline in renal function and lead to a poor pregnancy outcome

Chronic kidney disease is often clinically and biochemically silent until renal impairment is advanced. Symptoms are unusual until the glomerular filtration rate declines to <25% of normal, and more than 50% of renal function can be lost before serum creatinine rises above 120 µmol/l. Women who become pregnant with serum creatinine values above 124 µmol/l have an increased risk of accelerated decline in renal function and poor outcome of pregnancy (see Scenario box).[1-4w1] Several factors must be considered when managing pregnant women with chronic kidney disease to minimise the adverse effects of pregnancy on maternal renal function and the consequent effects on the fetus.

How common is chronic kidney disease in pregnancy?

Chronic kidney disease is now widely classified into five stages according to the level of renal function (table 1).[w2] Stages 1 and 2 (normal or mild renal impairment with persistent albuminuria) affect up to 3% of women of child bearing age (20-39 years).[w3] Stages 3-5 (glomerular filtration rate <60 ml/min) affect around one in 150 women of childbearing age,[w3] but because of reduced fertility and an increased rate of early miscarriage, pregnancy in these women is less common. Studies of chronic kidney disease in pregnancy have mostly classified women on the basis of serum creatinine values, but we estimate that around one in 750 pregnancies is complicated by stages 3-5.[w4] Some women are found to have chronic kidney disease for the first time during pregnancy. Around 20% of women who develop early pre-eclampsia (≤30 weeks' gestation), especially those with heavy proteinuria, have previously unrecognised chronic kidney disease.[w5]

Methods

Evidence for this review came from Medline and Cochrane database searches, as well as the authors' reference archives.

How do physiological changes of pregnancy affect the kidney?

The kidneys undergo pronounced haemodynamic, renal tubular, and endocrine changes during pregnancy (figure; table 2).[5w6] During healthy pregnancy the kidney increases production of erythropoietin, active vitamin D, and renin.[6]

From early pregnancy, increased renal blood flow leads to an increase in glomerular filtration rate of more than 50% (figure). Gestational hyperfiltration is accompanied by a relative decrease in concentrations of serum creatinine and urea, so values considered normal in the non-pregnant state may be abnormal in pregnancy (table 2). The plethoric kidneys appear larger on ultrasonography and—combined with renal pelvis and ureteric dilatation—these normal changes seen in pregnancy mimic outflow obstruction.[w7] A 5-10 g/l fall in plasma albumin, a rise in serum cholesterol, and oedema in late pregnancy can also occur in normal pregnancy, and sometimes simulate nephrotic syndrome.

Can diseased kidneys tolerate normal physiological changes of pregnancy?

Women with chronic kidney disease are less able to make the renal adaptations needed for a healthy pregnancy. Their inability to boost renal hormones often leads to normochromic normocytic anaemia, reduced expansion of plasma volume, and vitamin D deficiency.[6] The gestational rise in glomerular filtration rate is blunted in women with moderate renal

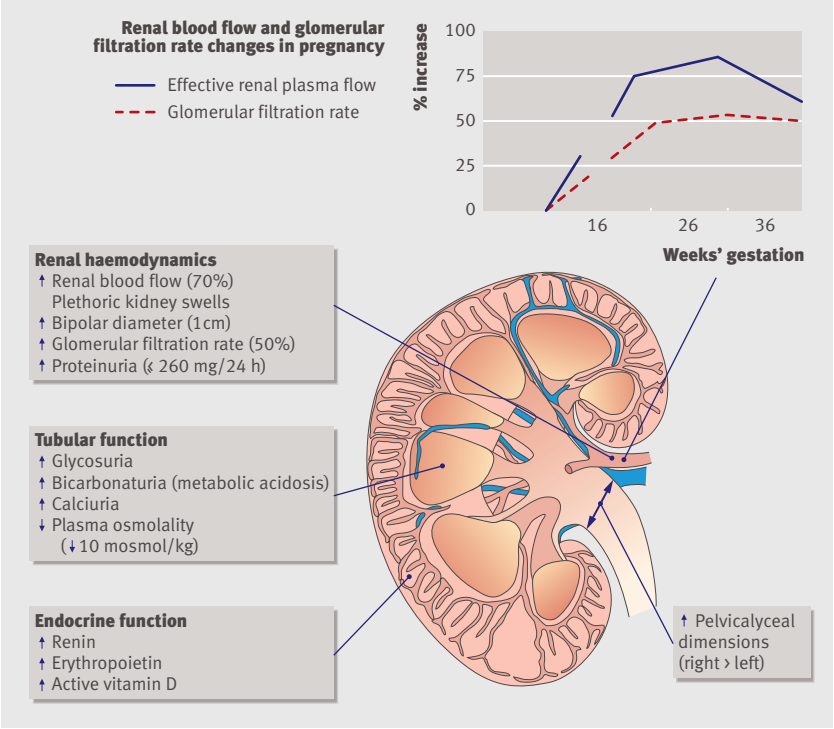
Table 1 | Stages of chronic kidney disease[w2]

Stage	Description	Estimated GFR (ml/min/1.73 m²)
1	Kidney damage with normal or raised GFR	≥90
2	Kidney damage with mildly low GFR	60-89
3	Moderately low GFR	30-59
4	Severely low GFR	15-29
5	Kidney failure	<15 or dialysis

GFR=glomerular filtration rate.

References w1 to w33 are on bmj.com

This is one of a series of occasional articles about how to manage a pre-existing medical condition during pregnancy.



Physiological changes to the kidney during healthy pregnancy

impairment and usually absent in those with a serum creatinine higher than 200 µmol/l.[4 7 8] If pre-eclampsia develops, maternal renal function often deteriorates further, but the addition of a prerenal insult that will reduce renal blood flow, such as peripartum haemorrhage or regular use of a non-steroidal anti-inflammatory drug, can seriously threaten maternal renal function. In such circumstances, nephrotoxic drugs must be avoided and maternal circulation restored with careful fluid management, as women with pre-eclampsia are prone to pulmonary oedema.

How does pregnancy affect maternal kidney function?

Mild renal impairment (stages 1-2)

Most women with chronic kidney disease who become pregnant have mild renal dysfunction and pregnancy does not usually affect renal prognosis (table 3). A case-control study of 360 women with primary glomerulonephritis and mild renal dysfunction (serum creatinine <110 µmol/l), minimal proteinuria (<1 g/24 h), and absent or well controlled hypertension before pregnancy showed that pregnancy had little or no adverse effect on long term (up to 25 years) renal function in the mother.[9] The situation is different for women with moderate to severe renal impairment.

Moderate to severe renal impairment (stages 3-5)

Small mainly uncontrolled retrospective studies have shown that women with the worst renal function before pregnancy are at greatest risk of an accelerated decline in renal function during pregnancy (table 3). Pre-existing proteinuria and hypertension both increase this risk.[2 4 8w17 w18] A retrospective series of women with chronic kidney disease (87 pregnancies) found that those who initially had moderate renal impairment (serum creatinine 124-168 mmol/l) had a 40% risk of a decline in renal function during pregnancy, which persisted after birth in about half of those affected.[3] However, 13 of 20 women with severe renal impairment (serum creatinine >177 mmol/l) had a decline in renal function during the third trimester, which persisted in most women and deteriorated to end stage renal failure in seven.[3w1]

A prospective study assessing the rate of decline of maternal renal function during pregnancy in 49 women with chronic kidney disease stages 3-5 before pregnancy confirmed these earlier observations.[2] Women with both an estimated glomerular filtration rate <40 ml/min/1.73 m^2 and proteinuria >1 g/24 h before pregnancy showed an accelerated decline in renal function during pregnancy.[2] Chronic hypertension predisposes women to pre-eclampsia—this may explain why some women with milder renal dysfunction also have a gestational decline in renal function.[2 3] The risk of such a decline is reduced when hypertension is controlled.

How does chronic kidney disease affect pregnancy outcome?

Maternal hypertension, proteinuria, and recurrent urinary tract infection often coexist in women with chronic kidney disease, and it is difficult to tell how

Table 2 | Physiological changes in common indices of renal function during healthy pregnancy. Values are mean (SD)[5 w6]

Measure	Stage of pregnancy			
	Before pregnancy	First trimester	Second trimester	Third trimester
Effective renal plasma flow (ml/min)	480 (72)	841 (144)	891 (279)	771 (175)
Glomerular filtration rate (ml/min) measured by inulin clearance	105 (24)	162 (19)	174 (24)	165 (22)
Glomerular filtration rate (ml/min) measured by 24 h creatinine clearance	98 (8)	151 (11)	154 (15)	129 (10)
Serum creatinine (µmol/l)	73 (10)	60 (8)	54 (10)	64 (9)
Plasma urea (mmol/l)	4.3 (0.8)	3.5 (0.7)	3.3 (0.8)	3.1 (0.7
Plasma urate (µmol/l)	246 (59)	189 (48)	214 (71)	269 (56)
Plasma osmolality (mosmol/kg)	290 (2)	280 (3)	279 (3)	279 (5)
Fasting cholesterol (mmol/l)	5.0 (0.3)	5.5 (0.4)	6.9 (0.4)	7.8 (0.4)

SCENARIO

A 37 year old woman with a history of reflux nephropathy and recurrent urinary tract infections presented for prepregnancy counselling with a serum creatinine of 153 µmol/l, hypertension controlled with ramipril 5 mg daily, and proteinuria of 1.4 g/24 h. The effect of pregnancy on her renal function and the increased risk of complications during pregnancy were explained. She was advised to take folic acid 400 µg daily and as soon as she knew she was pregnant to stop ramipril and start low dose aspirin (75 mg daily) to reduce the risk of pre-eclampsia.

She presented again 18 months later at 10 weeks' gestation. Her blood pressure was 144/92 mm Hg with no antihypertensives, serum creatinine was 136 µmol/l, and she had an asymptomatic urinary tract infection with *Escherichia coli*. The infection was treated with cefalexin 500 mg three times daily for seven days, and prophylactic cefalexin 125 mg nightly was continued for the rest of the pregnancy. Thromboprophylaxis with low molecular weight heparin (enoxaparin 40 mg daily) was started because of the prothrombotic effect of proteinuria (>1 g/24 h) and pregnancy. At 28 weeks, her blood pressure was 152/98 mm Hg and she was treated with nifedipine SR 10 mg twice daily. At 29 weeks, her blood pressure rose to 166/104 mm Hg, despite increased nifedipine SR 20 mg twice daily, and her renal function started to deteriorate (serum creatinine 188 µmol/l). Pre-eclampsia was diagnosed from the rise in blood pressure, raised liver transaminases (alanine transaminase 147 IU/l, aspartate transaminase 96 IU/l), and fall in platelet count (to 82×10^9/l). Fetal growth was at the fifth centile and had been reviewed with ultrasound every two weeks since 24 weeks' gestation. A caesarean section was carried out at 30+2 weeks because of signs of fetal distress and worsening maternal pre-eclampsia and renal function (serum creatinine 209 µmol/l), and a 1.1 kg baby boy was delivered.

Six months later, maternal renal function had not recovered to prepregnancy levels (serum creatinine 193 µmol/l). Hypertension was treated with ramipril and nifedipine SR. The baby was doing well, although he was still small for age.

much each of these factors contributes to a poor pregnancy outcome. It seems, however, that each factor is individually and cumulatively detrimental to fetal outcome.[2-4 6-8w1]

Women with severe renal impairment have the greatest difficulty conceiving, the highest rate of miscarriage, and the poorest pregnancy outcome.[1-4 7 8] The degree of renal dysfunction correlates with the risk of a poor pregnancy outcome (table 3).

How should chronic kidney disease be managed in pregnancy?

All women with chronic kidney disease should be referred early in pregnancy to an obstetrician and other specialist as necessary, to plan subsequent antenatal care. However, with a few exceptions, the most important aspects of managing chronic kidney disease in pregnancy relate to managing associated clinical features, rather than the type of kidney disease. Regular monitoring of maternal renal function (serum creatinine and serum urea), blood pressure, midstream urine (for infection), proteinuria, and when appropriate ultrasound (to detect urological obstruction) should identify pathological changes and allow timely intervention to optimise perinatal outcome and maternal renal outcome (table 4).

Before pregnancy

Ideally, all women with chronic kidney disease should be made aware of the risks to their long term renal function and to the fetus before they conceive (table 3). Women with chronic kidney disease often have amenorrhoea but may still occasionally ovulate and thus conceive. Contraceptive measures that consider clinical comorbidities should be taken by those who do not wish to become pregnant.

Folic acid 400 µg daily should be given as usual before conception until 12 weeks' gestation. Low dose aspirin (50-150 mg/day) should be started in early pregnancy to reduce the risk of pre-eclampsia and improve perinatal outcome.[10] Regular drugs should be reviewed. Fetotoxic drugs—such as angiotensin converting enzyme inhibitors and angiotensin II receptor blockers—should be stopped before pregnancy if equally effective drugs are available, or as soon as pregnancy is confirmed, if they are thought to be important for protecting maternal renal function.[w22]

During pregnancy

Chronic kidney disease includes a wide range of different conditions, and monitoring during pregnancy must be tailored to the severity of the disease and its complications (tables 4, 5). In general, all clinical and biochemical features should be checked more often as pregnancy progresses or if changes suggest deteriorating kidney function. Specialist care should begin early in pregnancy, but much of the monitoring of women with stage 1-2 disease can be done by primary care doctors.

When should specialists be involved?

Optimal management of pregnant women with chronic kidney disease often involves the combined expertise of specialists in obstetrics, nephrology, urology, fetal medicine, and neonatology. Impressive improvements in perinatal outcome over recent

Table 3 | Estimated effects of prepregnancy renal function on pregnancy outcome and maternal renal function. Values are the estimated percentage of women or neonates affected

Mean (SD) prepregnancy serum creatinine value (µmol/l)	Effects on pregnancy outcome				Loss of >25% renal function		
	Fetal growth restriction	Preterm delivery	Pre-eclampsia	Perinatal deaths	During pregnancy	Persists postpartum	End stage renal failure after 1 year
<125	25	30	22	1	2	0	0
125-180	40	60	40	5	40	20	2
>180	65	>90	60	10	70	50	35
On dialysis	>90	>90	75	50*	N/A	N/A	N/A

N/A=not applicable.
Estimates are based on literature from 1985-2007, with all pregnancies attaining at least 24 weeks' gestation.[1-4 7 8 w8-w16]
*If conceived on dialysis, 50% of infants survive; if conceived before introduction of dialysis, 75% of infants survive.

Table 4 | Care of women with chronic kidney disease during pregnancy

Measure	Details of monitoring
Urine	Every 4-6 weeks check for (1) infection—keep urine sterile with prophylactic antibiotics after one urinary tract infection[w19]; (2) proteinuria—use thromboprophylaxis with low molecular weight heparin if >1 g proteinuria/24 h; (3) haematuria—if present, perform microscopy for red cell casts, which suggest active renal parenchymal disease. Normal red cell morphology suggests urological pathology—seek urological advice
Blood pressure	Check blood pressure regularly, depending on how well blood pressure is controlled. Aim to keep it between 120/70 mm Hg and 140/90 mm Hg with antihypertensive treatment. Inappropriately low blood pressure is associated with fetal growth restriction, high blood pressure is associated with renovascular damage
Renal function	Check serum creatinine and urea, depending on stage of disease.* More frequently for disease stages 3-5 and in the second half of pregnancy
Full blood count	Check haemoglobin and recognise the need for iron (serum ferritin) and erythropoietin to keep haemoglobin at 100-110 g/l[w20]
Ultrasound of renal tract	Perform baseline renal ultrasound at booking (around 12 weeks' gestation) for pelvicaliceal dimensions. Repeat if symptoms suggest obstruction

*UK laboratories have been encouraged to report estimated glomerular filtration rate using the validated modification of diet in renal disease formula, whereby serum creatinine is adjusted for age, sex, and race. In pregnancy, however, this formula significantly underestimates the rate and cannot be recommended for use in clinical practice.[w21]

decades have been driven by advances in all of these specialties.[2-4w1] Sonographic assessment of uterine artery blood flow at 20-24 weeks' gestation can refine the risk of later pre-eclampsia and fetal growth restriction.[w32] Difficult decisions about the timing of delivery and managing renal function in women with kidney transplants and systemic disorders such as systemic lupus erythematosus and other vasculitidies require expert management.[6] Urological expertise is necessary for the management of obstructive disorders involving renal stones, congenital pelvo-ureteric abnormalities, or rare gestational obstructive disorders.[6] Maternal renal conditions with a genetic basis sometimes require specialist fetal medicine or genetic advice. The most common inherited renal condition, autosomal dominant polycystic kidney disease, is passed on to 50% of offspring.

Postpartum care

It can take up to three months, occasionally longer, for the physiological changes of pregnancy to disappear. During that time, close monitoring of fluid balance, renal function, blood pressure, and a further review of drug treatment are necessary. Women who have new onset proteinuria associated with pre-eclampsia should be followed until proteinuria disappears, or until a diagnosis of renal disease is made.

Breast feeding should be encouraged in women with chronic kidney disease. Information is confusing as to the extent to which some immunosuppressive drugs—such as ciclosporin and tacrolimus—appear in breast milk,[w33] but prednisolone, azathioprine, and angiotensin converting enzyme inhibitors are barely detectable in breast milk. It is still unclear whether the benefits of breast feeding are countered by neonatal absorption of immunosuppressive drugs. We generally encourage mothers who want to breast feed but are taking immunosuppressive drugs to do so as long as the baby is thriving.

Conclusions

Women with chronic kidney disease who become pregnant usually have mild renal dysfunction (stages 1-2) and have an uneventful pregnancy and good renal

Table 5 | Summary of important points regarding specific kidney diseases during pregnancy

Condition	Possible complications that need monitoring	Key management points
Primary glomerulonephritis	Hypertension; proteinuria; recurrent infection	Treat associated clinical features; outcome relates to control of clinical features and severity of renal impairment
Autosomal dominant polycystic kidney disease	Impaired renal function; hypertension	Make parents aware that the child has a 50% risk of inheriting the condition[w23]
Congenital urinary tract obstruction	Increased risk of urinary tract obstruction, even if previously surgically corrected[w24]	Perform kidney ultrasound in early pregnancy; serial assessment of renal function, urine culture, and blood pressure; repeat ultrasound if abnormalities in monitored parameters
Vesicoureteric reflux nephropathy	Recurrent urinary tract infections[w24]; ureteral obstruction; pre-existing renal impairment; hypertension	Prophylactic antibiotics may be needed; drainage of obstruction may also be necessary
Nephrolithiasis	Renal colic[w25]; ureteric obstruction	Magnetic resonance urography can be used in diagnosis to avoid exposure to radiation[w26]
Diabetic nephropathy	Declining renal function in women with pre-existing diabetic nephropathy[w27]; hypertension and proteinuria	Try to maintain good glycaemic control before, during, and after pregnancy
Nephritis caused by systemic lupus erythematosus	Can present like pre-eclampsia so investigate for distinguishing clinical and immunological features[w28]	Drug treatment managed by rheumatologist and obstetrician
Dialysis	Adjust dialysis to mimic the physiological changes of pregnancy[w29]	Haemodialysis is more effective than peritoneal dialysis at mimicking physiological change
Renal transplant	Pre-eclampsia; fetal growth restriction; deteriorating graft function[w30]	Delay pregnancy until graft function and immunosuppression are stabilised[w31]

outcome. Clinical features, in particular uncontrolled hypertension, heavy proteinuria (>1 g/24 h), and recurrent urinary tract infections have an independent and cumulative negative effect on the outcome of pregnancy. Women with moderate to severe disease (stages 3-5) are at highest risk of complications during pregnancy and of an accelerated decline in renal function. Successful management of women with chronic kidney disease during pregnancy requires team work between primary care clinicians, midwives, specialists, and the patient. Frequent monitoring of simple clinical and biochemical features will guide timely expert intervention to achieve optimal pregnancy outcome and conservation of maternal renal function.

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CHANGE PAGE

Patients with suspected rheumatoid arthritis should be referred early to rheumatology

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Change Page aims to alert clinicians to the immediate need for a change in practice to make it consistent with current evidence. The change must be implementable and must offer therapeutic or diagnostic advantage for a reasonably common clinical problem. Compelling and robust evidence must underpin the proposal for change.

The clinical problem

Rheumatoid arthritis affects 1% of adults and is associated with progressive joint damage and disability and increased mortality. Treatment with disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, has been shown to reduce the progression of radiologically evident joint damage and improve long term disability. A shift towards starting DMARD treatment as early as possible has therefore occurred. Guidelines recommend that patients should be referred early, ideally within six weeks of the onset of symptoms,[1] and that DMARDs should be started within 12 weeks of onset.[2] However, a recent survey found that only 50% of patients were assessed by a rheumatologist within this time.[3] I propose that patients with suspected rheumatoid arthritis should be referred to rheumatology as soon after first presentation as possible.

Evidence for change

Benefits of early treatment:

A recent meta-analysis of 12 studies (six open label extensions of randomised controlled trials and six observational cohort studies) examined the association between delay to DMARD treatment and radiological progression in patients with early rheumatoid arthritis (<2 years at presentation).[4] The average time between early and delayed treatment was nine months. After a median of three years of observation, patients who received early treatment had 33% less progression than delayed patients.

A second meta-analysis of 14 randomised controlled trials of DMARD treatment in rheumatoid arthritis found that the strongest predictor of improvements in disease activity (according to the American College of Rheumatology definition[5]) was shorter disease duration at start of treatment. The best response was in patients treated within a year of symptom onset.[6]

The very recent PROMPT trial compared methotrexate and placebo in 110 patients with undifferentiated polyarthritis (not yet fulfilling criteria for established rheumatoid arthritis).[7,8] The median disease duration was nine months. The trial concluded that treatment with methotrexate delayed the onset of

Methods

I searched Medline (1950 to May 2007) with the following MeSH headings: "rheumatoid arthritis", "antirheumatic agents", and "treatment outcome", as well as the key words "early" and "delay". In addition, I reviewed bibliographies of identified papers and recent treatment guidelines.